

**REMARKS**

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

**I. CLAIM STATUS & AMENDMENTS**

Claims 1 and 2 were pending in this application when last examined and stand rejected.

Support for the amendment to claim 1 can be found, for example, in the disclosure at page 3, lines 1-16, Example 2 at page 7 and original claim 1.

Applicants reserve the right to file a continuation or divisional application on any cancelled subject matter.

**II. WRITTEN DESCRIPTION REJECTION**

In item 3 on page 2, claims 1 and 2 were newly rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement on the basis the Specification lacks support for “wherein the antigenic protein is not naturally present on the surface of a cell” in claim 1.

The present amendment overcomes this rejection.

Applicants again respectfully submit the Specification provides full written support for and clearly defines the language “wherein the antigenic protein is not naturally present on the surface of a cell” in claim 1. As noted in the last response filed April 11, 2006, support for such can be found, for instance, in Example 2, which discloses nuclear protein HP10496 as a specific example of an antigenic protein not naturally present on the surface of a cell, supported claiming all antigenic proteins not naturally present on the surface of a cell.

Nonetheless, without intending to acquiesce to the rejection and for the sole purpose of expediting prosecution, claim 1 has been amended to delete the objected language of “wherein the antigenic protein is not naturally present on the surface of a cell”.

Therefore, the written description rejection of claims 1 and 2 under 35 U.S.C. § 112, first paragraph, is now untenable and should be withdrawn.

### **III. INDEFINITENESS REJECTION**

In item 5 on pages 2-3, claims 1 and 2 were again rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the recitation of “wherein the antigenic protein is not naturally present on the surface of a cell.”

For the same reasons set forth, it is respectfully submitted that the present amendment overcomes this rejection. Again, without intending to acquiesce to the rejection and for the sole purpose of expediting prosecution, claim 1 has been amended to delete the objected language of “wherein the antigenic protein is not naturally present on the surface of a cell”.

In view of the above amendment, the rejection of claims 1 and 2 under 35 U.S.C. § 112, second paragraph, is now untenable and should be withdrawn.

### **IV. OBVIOUSNESS REJECTION**

In item 8 on pages 3-5, claims 1 and 2 remained rejected under 35 U.S.C. 103(a) as being obvious over Scholler et al. (US 2003/0008342) in view of Yokoyama-Kobayashi et al. (Gene, Vol. 228, No. 1-2, pp. 161-167, March 1999).

Applicants respectfully traverse this rejection as applied to the amended claims.

To establish obviousness, three criteria must be met. First, the prior art references must teach or suggest each and every element of the claimed invention. M.P.E.P. § 2143.03. Second, there must be some suggestion or motivation in the references to either modify or combine the reference teachings to arrive at the claimed invention. M.P.E.P. § 2143.01. Third, the prior art must provide a reasonable expectation of success. M.P.E.P. § 2143.02.

The novelty of the present invention is that “the C-terminal side of the transmembrane domain and the antigenic protein are outside of the cell.” This means that a part of the

transmembrane domain (C-terminal side thereof) and the antigenic protein are outside of the cell, and hence the “whole of the antigenic protein” is extracellularly expressed. No part of the antigenic protein is therefore anchored in the cell membrane.

This feature is reflected in amended claim 1, which calls for a method for producing an antibody, which method comprises: inoculating an animal with an expression vector expressing a fusion protein comprising an antigenic protein fused with the C-terminal of a transmembrane domain, wherein when the fusion protein is expressed, the N-terminal side of the transmembrane domain is located in the cell and the C-terminal side of the transmembrane domain and the antigenic protein are outside of the cell; and isolating an antibody against the antigenic protein from the animal and purifying the antibody.

This aspect of the invention is neither disclosed or suggested in the combined teachings of Scholler et al. and Yokoyama-Kobayashi et al. In addition, the cited references fail to provide a reasonable expectation of success for combining/modifying their teachings to arrive at this aspect of the invention.

The invention in Scholler et al. aims to elicit or enhance the titer of antibodies specific for a cell surface receptor antigen (SRA). Scholler et al. discloses the possibility of “membrane localization” of an antigen for immune response (antibody production). In particular, Scholler et al. suggest the use of transmembrane domain for causing the SRA to localize to the cell surface. In the last response, it was noted that Scholler et al. do not show a concrete example of using transmembrane domain for the membrane localization. In other words, Scholler et al. do not present concrete examples for the use of a transmembrane domain in the claimed method for producing antibodies. Accordingly, the teaching in Scholler et al. merely amounts to an uncertain suggestion. Thus, the only achievement assured of in Scholler et al. is expression of a naturally present SRA together with a first and second immune response altering molecules.

The Office replied by arguing that “concrete examples” are not required to provide enablement of a US patent application or prior art reference.

In reply thereto, it is respectfully submitted that the lack of concrete examples is a factor to consider, especially when the combined cited prior art lacks a reasonable expectation of success, as in the case as discussed below.

A concrete example of the membrane localization in the art field is found in Boyle et al.

However, as noted in the last response, Boyle et al. clearly suggest that the membrane localization has disadvantages in terms of immune response (see, for example, Abstract).

Boyle et al. was previously submitted as evidence of the lack of a reasonable expectation of success in the art for producing antibodies using a fusion between a transmembrane domain and an antigenic protein, because based on the state of the art and the uncertain suggestion in Scholler et al., such a fusion would decrease antibody production (which contravenes the purpose of the invention).

Again, Boyle et al. is evidence that at the time of filing of the application, it was believed that antibody titer decreases when using an antigenic protein, which has been converted into a membrane type by fusion with transmembrane domain. See again page 2, lines 13-20 of the specification and the Boyle reference (Int. Immunol., vol. 9, no. 12, pp. 1897-1906, 1997) discussed therein. Such an understanding clearly indicates the lack of reasonable expectation of success in the combined teachings. In fact, such an understanding would lead the skilled artisan away from the combination of Scholler et al. and Yokoyama-Kobayashi et al.

Further, in Boyle et al., the OVA (antigenic protein) is attached to the C-terminal side of the transmembrane part (the transferrin receptor portion). Thus, the OVA is at the C-terminal end of the fusion protein. This is the same as the present invention.

Since the mOVA in Boyle et al. is on the surface of the cell (see page 1899 under the result section), Boyle et al. appears to teach that the C-terminal end of the fusion (the antigenic part) is outside of the cell. This may also be the same as the present invention.

However, despite the similarity, Boyle et al. discloses that the membrane localization of antigen for immune response provides negative results, whereas, the present invention clearly shows positive results.

Again, prior to the instant invention as evidence by Boyle et al, it was reported that as an example of gene immunization, ovalbumin was fused to the downstream portion of a transmembrane domain of transferrin receptor to form a membrane type. When this fusion protein was injected intramuscularly or subcutaneously into mice for the purpose of investigating the effect of the expression site of the antigenic protein on the efficacy of gene immunization, the antibody titer actually decreased, because the protein was converted into a membrane type. This stands in contrast to the present invention, which clearly shows positive results.

In contrast to the results in Boyle et al., Applicants succeeded by fusing a non-membrane type antigenic protein with the C-terminal of the transmembrane domain, thereby localizing the protein to the cell surface. This feature of the claimed invention was neither disclosed nor suggested by the cited prior art references, and there was no reasonable expectation of success in the prior art for modifying the prior art teachings for doing so.

The present inventors assumed the negative results of Boyle et al. might be due to the fact that the antigenic part (OVA) is not wholly extracellularly expressed and is “membrane type” protein. This assumption was correct. The antigenic protein, which is wholly extracellularly expressed, produces more antibodies than the secreted antigen or the intracellular antigen.

Scholler et al. do not disclose this inventive concept of the instant invention.

Accordingly, there was no reasonable expectation of success in the art for producing antibodies using a fusion between a transmembrane domain and an antigenic protein that is not naturally present on the surface of a cell, because based on the state of the art and the uncertain suggestion in Scholler, such a fusion would decrease antibody production.

Yokoyama-Kobayashi et al. fail to remedy the deficiencies in Scholler et al.

Though Yokoyama-Hashimoto et al. teach the claimed vector can be used to produce a fusion protein that can be used to anchor a secreted molecule to the cell surface, Yokoyama-Hashimoto et al. do not disclose that the claimed vector can express the fusion protein in a wholly extracellular mode.

Therefore, it is respectfully submitted that the present invention is neither disclosed nor suggested from the combined disclosures of Scholler et al. and Yokoyama-Hashimoto et al. and the cited references lack a reasonable expectation of success of combining and/or modifying their teachings to arrive at the claimed invention.

In view of the above, the rejection of claims 1-4 under 35 U.S.C. § 103(a) over Scholler (US 2003/0008342) in view of Yokoyama-Kobayashi is untenable and should be withdrawn.

#### CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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